Cerebral blood flow in striatal regions is associated with apathy in patients with schizophrenia

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Abstract: BACKGROUND Striatal dysfunction has been proposed as a pathomechanism for negative symptoms in schizophrenia. There is consensus that negative symptoms can be grouped into 2 dimensions: apathy and diminished expression. Recent studies suggest that different neural mechanisms underlie these dimensions, but the relationship between regional resting-state cerebral blood flow (rCBF) and negative symptom dimensions has not been investigated. METHODS This study included 29 patients with schizophrenia and 20 healthy controls. We measured rCBF in the striatum using arterial spin labelling (ASL) MRI. We assessed negative symptoms using the Brief Negative Symptom Scale. RESULTS In the ventral and dorsal striatum, rCBF was not different between patients with schizophrenia and controls. However, we did find a positive association between the severity of apathy and increased rCBF in the ventral and dorsal striatum in patients with schizophrenia. This effect was not present for diminished expression. LIMITATIONS All patients were taking atypical antipsychotics, so an effect of antipsychotic medication on rCBF could not be excluded, although we did not find a significant association between rCBF and chlorpromazine equivalents. CONCLUSION The main finding of this study was a specific association between increased striatal rCBF and the negative symptom dimension of apathy. Our results further support the separate assessment of apathy and diminished expression when investigating the neural basis of negative symptoms. The ASL technique can provide a direct and quantitative approach to investigating the role of rCBF changes in the pathophysiology of negative symptoms.

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Cerebral blood flow in striatal regions is associated with apathy in patients with schizophrenia

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Abstract

Background: Striatal dysfunction has been proposed as a pathomechanism for negative symptoms in schizophrenia. There is consensus that negative symptoms can be grouped into the two dimensions *apathy* and *diminished expression*. Recent studies suggest that different neural mechanisms underlie these dimensions, however, the relationship between regional resting-state cerebral blood flow (rCBF) and negative symptom dimensions has not been investigated.

Methods: 29 patients with schizophrenia and 20 healthy controls were included. rCBF in the striatum was measured using arterial spin labeling (ASL) magnetic resonance imaging. Negative symptoms were assessed using the Brief Negative Symptom Scale.

Results: The rCBF in the ventral and dorsal striatum was not different between patients with schizophrenia and controls. However, in the patients a positive association between the severity of apathy and increased rCBF in the ventral and dorsal striatum was found. This effect was not present for diminished expression.

Limitations: Since all patients were medicated with atypical antipsychotics, an impact of antipsychotic medication on rCBF cannot be excluded, although we did not find a significant association between rCBF and chlorpromazine equivalents.

Conclusion: The main finding of this study is a specific association between increased striatal rCBF and the negative symptom dimension of apathy. Our results further support a separate assessment of apathy and diminished expression when

investigating the neural basis of negative symptoms. ASL can provide a direct and quantitative technique to investigate the role of rCBF changes in the pathophysiology of negative symptoms.

Introduction

Striatal dysfunction has been hypothesized to be a fundamental mechanism underlying symptoms of schizophrenia for decades.[1] A robust finding in the literature regards an increased striatal dopamine synthesis in schizophrenia measured with positron emission tomography and single-photon emission computed tomography.[2,3] Studies using functional magnetic resonance imaging (fMRI) to assess striatal response to rewards have shown a decreased signal in unmedicated patients.[4-6] Results in medicated patients are heterogenous,[7-9] indicating a complex relationship between dopamine dysregulation and fMRI findings.

More recently, it has been suggested that an increase in dopamine turnover could be accompanied by an increased perfusion of striatal areas.[10,11] Arterial spin labeling imaging (ASL) allows to obtain an absolute measure of regional cerebral blood flow (rCBF). Previous studies indeed suggest an increase in striatal rCBF in patients with schizophrenia[11-14] and a high risk for psychosis,[15] but findings are not fully consistent[11,16-18] and further research is clearly needed.

Schizophrenia is a disorder with heterogeneous symptom expression along its course and negative symptoms have been found to have a strong impact on long-term morbidity and poor functional outcome.[19,20] There is now a consensus that negative symptoms can be dissociated into two dimensions: [21-23] A motivational dimension consists of anhedonia, avolition and asociality and will be referred to as *apathy*. The second

dimension *diminished expression* combines the symptoms blunted affect and alogia. In fMRI studies an association of ventral striatal hypoactivation with negative symptoms, in particular apathy, has repeatedly been reported.[8,24-26] In addition, a recent study found an association of dorsal striatal hypoactivation in response to reward and apathy.[27]

It has to be kept in mind that these fMRI results do not reflect absolute hypoactivation in the striatum, but a decreased signal difference between rewarding and non-rewarding stimuli. Therefore, the absolute measure of rCBF provided by ASL can offer additional information on the neural basis of symptoms. Most studies investigating ASL have not focused specifically on the striatum, but have used whole brain analysis approaches.[12,14,28] Nevertheless, a few studies have reported associations of striatal rCBF with symptoms: Kindler et al.[11] showed a positive correlation between striatal rCBF and positive symptoms in patients with treatment resistant auditory hallucinations. Zhuo et al.[16] found increased rCBF in striatal and auditory areas in patients with auditory verbal hallucinations.

In addition to these ASL studies on rCBF in the striatum, earlier PET studies have reported an association of negative symptoms with reduced rCBF at rest and during an attentional task in frontal and parietal regions.[29-31] However, these studies did not address the distinction between apathy and diminished expression. Liemburg et al.[32] found apathy to be related to abnormal activation in parietal and thalamic regions during a planning task, but did not specifically investigate striatal

rCBF. Overall, negative symptoms seem to be associated with reduced rCBF in particular in frontal regions, but regional specificity remains to be determined.

The main goal of this study was to investigate the association of striatal rCBF with negative symptoms. There is evidence that the two negative symptom dimensions apathy and diminished expression show differential associations with behavioral[33,34] and neurobiological correlates, suggesting differences in pathophysiology. Therefore, this distinction is of high relevance when investigating striatal rCBF. The paucity of reported associations of striatal rCBF with negative symptoms might result from the fact that until now apathy and diminished expression have not been addressed separately, although the striatum might play very different roles in their pathophysiology.

Based on the extant, albeit limited, evidence for increased striatal resting-state rCBF in patients with schizophrenia,[24,26] our first hypothesis was that these patients would show increased rCBF in the ventral and dorsal striatum compared to controls. Our second and main hypothesis was that the negative symptom dimension apathy would be associated with altered rCBF in the ventral and dorsal striatum. As no study has previously reported striatal rCBF in relation to specific dimensions of negative symptoms, no predictions of directionality of the effects could be made.

Methods

Participants

Twenty-nine patients with schizophrenia and twenty healthy controls matched on a group level for age and sex were included in the present study. Patients were recruited from outpatient and inpatient units of the Psychiatric Hospital of the University of Zurich and affiliated institutions. Healthy controls were recruited from the community via advertisement.

For confirmation of the diagnosis the Mini-International Neuropsychiatric Interview was conducted.[35] Patients were clinically stable and were under a stable dose of medication for at least two weeks prior to testing. Inpatients were at the end of their hospitalization engaging in a multimodal therapy program and activities outside the hospital. Please note that the average duration of hospitalization for patients with schizophrenia in Swiss psychiatric hospitals is longer than in most other countries, so the majority of patients would have been treated as outpatients in other health care systems. Exclusion criteria for patients were any other DSM-IV Axis I disorder, acute psychotic symptoms (i.e. scores higher than 4 on the positive subscale of the Positive and Negative Syndrome Scale [PANSS][36]), extrapyramidal side effects (i.e. a total score higher than 2 on the Modified Simpson-Angus Scale [MSAS][37]) and lorazepam medication higher than 1mg per day. If the criteria for abuse or dependency of cannabis were met, the patients were excluded from the study. Furthermore, participants were excluded, if they had any alcohol use disorder based on lifetime criteria.

Smoking was not an exclusion criterion, but participants did not smoke for two hours before the ASL-scans were conducted.

Healthy controls were excluded if any neuropsychiatric diagnosis was present in the structured Mini-International Neuropsychiatric Interview.[35] In both groups participants with neurological disorders were excluded.

The Ethics Committee of the Canton of Zurich approved the project and participants gave written informed consent to participation in the study. The capability of each participant with schizophrenia to give informed consent was evaluated by the treating psychiatrist.

Clinical and neuropsychological assessment

Negative symptoms were assessed using the Brief Negative Symptom Scale (BNSS).[38] The two factors of negative symptoms were calculated as follows: The apathy dimension consists of the anhedonia, avolition and asociality items and the diminished expression dimension includes the blunted affect and alogia items.[39] Other assessment instruments used were the PANSS,[36] the Calgary Depression Scale for Schizophrenia (CDSS),[40] the Global Assessment of Functioning Scale (GAF)[41] and the Personal and Social Performance Scale (PSP).[42] Cognition was assessed with a brief neurocognitive test battery (see our previous studies[33,34] for details), which was used to compute a composite cognitive ability score for each participant. The following domains were included in the battery: verbal

learning, verbal and visual short-term and working memory, processing speed, planning, and semantic and phonemic fluency.

MRI data acquisition

MR data were acquired on a Philips Achieva 3.0T whole-body scanner (Best, The Netherlands). We employed resting state pseudo-continuous ASL (pCASL) perfusion-weighted scans. Due to superior signal-to-noise ratio, pCASL is considered a more reliable method, compared to other ASL sequences.[43,44] The imaging parameters for the pCASL were based on the sequence developed by Dai et al., 2008.[45] The plane was positioned parallel to the imaging volume with a 20 mm labeling gap between the imaging volume and the labeling volume. ASL Parameters for the single shot gradient echo EPI sequence were: repetition time (TR): 4400 ms; echo time (TE): 20 ms; flip angle: 90°, FOV: 240 × 161 x 240 mm; spacing: 3 mm, matrix size: 80, 23 slices with slice thickness of 7 mm and no gap; SENSE 2.5; post-labeling delay of 1525 ms; label duration: 1650 ms; number of dynamics: 75 (duration 667.9 s). One dynamic consisted of a control and a labeled image. Additionally, high-resolution anatomical images (TR = 8.1 ms, TE: 3.7 ms, FOV = 240 x 240 mm^2, voxel size, 1 × 1 × 1 mm) were acquired using a standard T1-weighted 3D magnetization prepared rapid gradient echo sequence (MP-RAGE).

CBF calculation

Image data processing and analysis were performed using the ASLtoolbox[46] running in MATLAB (The MathWorks Inc., Natick, MA, 2000) and compatible with the Statistical Parametric Mapping software (SPM12, Wellcome Trust Centre for Neuroimaging, UK implemented in Matlab, Math Works, Natick, MA). For each participant, image preprocessing was conducted including realignment independently for labeled and unlabeled images, spatial smoothing (6 x 6 x 14 mm kernel), perfusion weighted image construction and calculation, and normalization to the Montreal Neurological Institute [MNI] template (for ASL data, rCBF calculations should be performed prior to spatial normalization[46]). Equilibrium brain tissue magnetization (M0) images were recorded in a separate run for each subject using the same parameters as described for the pCASL sequence, apart from the TR (10 s). Next, unique cerebral spinal fluid M0 values were calculated per participant for each session (and corrected for T2* decay using a T2* value of 74.9 ms) and the relevant H_2O partition coefficient was taken from the literature[47] and considered in the calculation of each perfusion weighted image. Perfusion weighted image series were generated by simple subtraction of the label and control images, followed by conversion to absolute mean rCBF image series.

Region of interest image analysis

Predefined regions of interest (ROIs) for the ventral and

dorsal striatum were derived based on previous key

publications using fMRI (see Fig. 1). As in the study of Yip and colleagues,[48] for the ventral striatum ROI coordinates (MNI) were defined according to a meta-analysis by Knutson and Greer[49] (left: *x*=−12, *y*=10, *z*=−2; right: *x*=10, *y*=8, *z*=0, both 9mm spheres), which have also been used in our previous studies.[25,50] Coordinates for the dorsal striatum ROI were also adopted from the recent study by Yip et al.[48] (left: *x*=−9, *y*=3, *z*=15; right: *x*=9, *y*=3, *z*=15, both 9mm spheres). The ROIs were generated with the Wake Forest University Toolbox.[51] For each ROI (VS-ROI, DS-ROI) mean rCBF was extracted using the MARSBAR toolbox (http://marsbar.sourceforge.net).

To compare the mean cortical (grey matter masked) CBF between groups, we extracted the mean CBF for each group from 90 cortical brain regions (AAL atlas, http://neuro.imm.dtu.dk/wiki/Automated_Anatomical_Labeling) and applied an unpaired two-tailed t-test.

Statistical analysis

Statistical analyses were computed using IBM SPSS Statistics version 22. Demographic comparisons were tested with a χ^2 test, t-tests and Mann-Whitney U-tests if the criterion of normal distribution was not met. To test our first hypothesis t-tests were calculated for group comparisons of rCBF between patients and controls for each ROI (ventral and dorsal striatum). Normal distribution was confirmed with a Shapiro-Wilk test and homogeneity of variances was tested using Levene's test. Both

assumptions were met in the current sample. Furthermore,

ANCOVAs were calculated to control for potential sociodemographic differences between the patient and control group.

To test the main hypothesis Spearman correlation coefficients (r_s) were calculated between negative symptoms (apathy and diminished expression) and rCBF in the ventral and dorsal striatum. A Steiger's z-test was used to test the difference between the two negative symptom dimensions as dependent variables and rCBF as the common independent variable.

To address potentially confounding factors in the patient group we calculated Spearman correlation coefficients between rCBF in the ventral and dorsal striatum and age, positive symptoms, chlorpromazine equivalents, depressive symptoms and cognitive impairments via the composite cognitive ability score. Only age showed a significant association with rCBF as well as apathy. Therefore, non-parametric partial correlations were calculated to account for the effects of age on the correlation between negative symptoms and rCBF.
All primary analyses reported above regard bilateral striatal regions, because we had no a priori hypotheses regarding differences between left and right striatum.

Results

Demographic and clinical characteristics

Demographic and clinical data are summarized in Table 1. The groups did not show significant differences with regard to age

and sex. Healthy controls had a higher educational level and cognitive scores.

The following antipsychotic monotherapies were taken by the patient group: Clozapine (2 patients), olanzapine (1 patient), quetiapine (2 patients) amisulpride (2 patients), risperidone (7 patients), paliperidone (2 patients), aripiprazole (2 patients). Several patients took a combination of antipsychotic medication: Clozapine and aripiprazole (1 patient), clozapine and amisulpride (1 patient), olanzapine and aripiprazole (1 patient), olanzapine and quetiapine (1 patient), olanzapine and risperidone (1 patient), amisulpride and quetiapine (1 patient), risperidone and quetiapine (3 patients), risperidone and aripiprazole (1 patient), aripiprazole and quetiapine (1 patient).

CBF differences between groups

To test our first hypothesis we compared rCBF between groups in the ventral and dorsal striatum. Patients and healthy controls did not differ significantly in rCBF in the ventral striatum and in the dorsal striatum (see Table 2). Thus, the hypothesis that patients with schizophrenia would show altered rCBF in the striatum could not be confirmed.

After controlling for educational level and cognitive score patients with schizophrenia showed a trend towards higher rCBF in the ventral striatum ($F(1,45)= 3.37$, $p= .07$), but not the dorsal striatum ($F(1,45)= 1.89$, $p= .18$).

To control for differences in total grey matter CBF between patients (m = 41.4 ml/100mg/min; SD = 8.8) and controls (m = 41.7 ml/100mg/min; SD = 8.7) a t-test was calculated, which showed no significant differences between groups (t (47) = .11; p = .91). We additionally addressed potential differences in total grey matter volume between patients (m = 671.8 mm^3; SD = 51.4) and controls (m = 677.7 mm^3; SD = 46.23), which showed no significant differences between groups (t (47) = .41; p = .68).

No participants had to be excluded because of excessive motion. Patients and control group did not differ significantly on motion parameters.

Correlation between CBF and negative symptoms

To test our main hypothesis we calculated Spearman correlations between rCBF of the striatum and the two negative symptom dimensions in the patient group (see Table 3). A significant positive correlation was found between the ventral striatal rCBF and apathy (see Fig. 2a and Table 3) as well as dorsal striatal rCBF and apathy (see Fig. 2b and Table 3). This finding provides evidence that patients with more apathy show higher rCBF in the striatum. No significant correlation was found between ventral striatum and diminished expression (see Fig. 2c and Table 3) and dorsal striatum and diminished expression (see Fig. 2d and Table 3). The results of Steiger's z-Test were nearly significant (ventral striatum: z= 1.88, p= .06; dorsal striatum: z= 1.73, p= .08). In other words, these results suggest that the correlation between rCBF and apathy

was stronger than the correlation between rCBF and diminished expression. Concerning the BNSS total score, we observed a trend-level correlation with rCBF in the dorsal striatum (r= .34; p= .07, df= 27), but not in the ventral striatum (r= .20; p= .29, df= 27).

rCBF did not correlate significantly with the following potentially confounding variables: PANSS positive factor, CDSS for depressive Symptoms, chlorpromazine equivalents, and the composite cognitive ability score (see Table 4). Significant positive correlations were found between age and rCBF of the ventral and dorsal striatum. Therefore, non-parametric partial correlations were calculated to control for effects of age on the correlation of rCBF with apathy. The association between apathy and rCBF in the dorsal striatum was at trend-level (r= .34, p= .08, df= 26), while the association with the ventral striatum was no longer significant (r= .25, p= .19, df= 26).

All primary analyses reported above regard bilateral striatal regions, because we had no a priori hypotheses regarding differences between left and right striatum. In an exploratory analysis we compared the associations of left and right striatum with apathy as well as diminished expression, which showed the same pattern of results as the bilateral analysis (see Table 3).

Furthermore, an exploratory voxel-wise analysis of rCBF in the prefrontal cortex and anterior cingulate cortex was performed. The statistical threshold was set at a peak-level family-wise error (FWE) rate correction of p = .05. We found no voxels to be significantly associated with apathy in the patient group.

Discussion

In the present study we observed no significant differences in striatal rCBF between patients with schizophrenia and healthy controls. Importantly, the negative symptom dimension apathy - but not diminished expression - was associated with dorsal striatal rCBF and to a lesser extent ventral striatal rCBF.

Our first hypothesis concerning group differences could thus not be confirmed. This is at odds with some studies reporting increased striatal rCBF in patients with schizophrenia[11,12,14,16] whereas other studies did not observe these effects.[17,18] Potential explanations for these differences between studies include differences in image acquisition and data analysis. Most importantly, the patient populations differ in numerous aspects. In our study inclusion and exclusion criteria were specified in order to primarily assess negative symptoms. Thus, our patients had low levels of positive symptoms. In contrast, patients in the Kindler et al.[11] study had treatment resistant auditory hallucinations. Another important factor might be the type of treatment with antipsychotic medication.[14,52,53] In our study all patients were treated with atypical antipsychotic medication which in fMRI studies has been shown to attenuate group differences in striatal activation.[4,8,25]

Regarding our main hypothesis the patient data showed a significant association between the severity of apathy and

rCBF of both ventral and dorsal striatum, a relationship that was not found for the symptom dimension of diminished expression. This differential effect for the two negative symptom dimensions might account at least in part for the lack of consistent previous findings regarding rCBF correlates of negative symptoms. In our study, an aggregation of overall negative symptoms would have led to a non-significant finding. The only other ASL study specifically assessing apathy concerns rCBF during planning task performance, during which reduced parietal and thalamic perfusion was observed.[32] However, striatal perfusion was not reported and the comparison with our resting state approach is difficult. It seems to be important for future ASL studies to assess both dimensions of negative symptoms separately since different neural mechanisms may be underlying these symptoms.[21,33,54]

While the distinction between the two negative symptom dimensions apathy and diminished expression has received very limited interest in previous ASL studies, the blood oxygen level dependent (BOLD)-fMRI literature has provided evidence for a dissociation of their neural correlates. For instance, Kirschner et al.[25] reported reduced activity in the ventral striatum during reward anticipation, which correlated with apathy, but not diminished expression. For the dorsal striatum an association between reduced activity and avolition, but not anhedonia, has been shown. Importantly, in these fMRI studies reduced activity reflects attenuated signal differences between rewarding and non-rewarding stimuli. Therefore, an association of apathy with both a reduced task-related fMRI

signal and increased resting-state rCBF in the striatum is not contradictory.

At this point a mechanistic explanation for the association of apathy and striatal rCBF remains somewhat speculative. Several studies found increased rCBF in the striatum to be related to higher dopaminergic activity.[55,56] In addition, one PET study reported an association of increased dorsal striatal dopamine release with negative symptoms,[57] which might seem at odds with the observation that decreased dopamine availability can lead to apathy in neurological patients and animal models.[57–59] However, the hypothesis of aberrant salience attribution in schizophrenia proposes that increased dopaminergic activity in the striatum leads to difficulties in distinguishing between relevant and irrelevant stimuli.[60,54] This model has also been employed to account for the attenuated striatal reward signal in fMRI studies that has been shown to be associated with negative symptoms.[61] Thus, this inability to differentiate relevant and in particular rewarding stimuli can potentially lead to a decrease in goal-directed behavior and promote apathy.[62]

We found no significant correlation between positive symptoms or cognition and striatal rCBF. Regarding positive symptoms it has to be kept in mind that the aim of the study was to investigate neural correlates of negative symptoms and patients with significant positive symptoms were excluded, thereby considerably reducing variance. Cognitive deficits were not an exclusion criterion, but patients had to be able to take part in this relatively demanding study and the

overall cognitive performance of the patient group was less than one standard deviation below the control group.

It may surprise that we did not find a significant group difference in rCBF of the striatum in spite of the relationship between apathy and striatal rCBF. It has to be noted that striatal rCBF was slightly higher in patients, although this difference was not significant. This type of pattern can best be explained by a difference between patients and controls that is only present for patients with a high level of apathy. In addition, treatment with antipsychotics might attenuate group differences in striatal rCBF to some extent.[63]

It is of note that we observed higher age to be associated with reduced striatal rCBF and lower apathy, although effects of age have not been reported in previous studies of patients with schizophrenia. However, our finding is consistent with previous reports of a reduction of rCBF with increasing age in healthy subjects.[64,65] Interestingly, a finding of a negative relationship between age and negative symptoms as well as white matter integrity measured by diffusion tensor imaging is discussed in a paper by Bijanki et al.,[66] that emphasizes the necessity to include age as a confounding variable. Our finding, that younger patients showed stronger apathy than older participants might seem somewhat surprising, but is consistent with the study by Bijanki and colleagues.[66] Overall, the inclusion of age in partial correlations of apathy and striatal rCBF attenuated the association, but the effect in the dorsal striatum remained at trend-level.

Limitations

This study provides evidence for a positive association between increased striatal rCBF and the negative symptom dimension of apathy. Several limitations have to be taken into account in the interpretation of these findings. First, sample size was moderate and our findings require replication in a larger sample, which would also allow to further specify the impact of age on the observed associations. Second, our sample was recruited with the aim of investigating neural correlates of negative symptoms and is thus not representative of the whole population of patients with schizophrenia. It is possible that different associations between symptoms and striatal rCBF can be found in patients with higher levels of positive or depressive symptoms. Third, all patients in our study took second-generation antipsychotic medication. Previous research has suggested an influence of antipsychotic medication on striatal rCBF.[52,63,67,68] While we did not observe an association of striatal rCBF and antipsychotic dose, this does not exclude a potential impact of antipsychotic medication. Thus, future studies should include non-medicated patients and patients taking first-generation antipsychotics to generalize the relationship between apathy and striatal activity to these populations.

Conclusion

The association between increased striatal rCBF and the negative symptom dimension of apathy, but not diminished expression, provides further evidence for the assumption of different underlying neural bases. Hence, these dimensions should be considered separately in future research on negative symptoms. Furthermore, ASL seems to provide a direct and quantitative technique to investigate negative symptoms circumventing the limitations of task based measures often employed for BOLD-fMRI and the invasiveness of positron emission tomography and single-photon emission computed tomography. This may qualify ASL as an alternative technique for developing biomarkers reflecting the pathomechanisms of negative symptoms.

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Contributors: M. Kirschner, M. N. Hartmann-Riemer, E. Seifritz, P. Stämpfli, P.N. Tobler and S. Kaiser designed the study. M. Kirschner and M. N. Hartmann-Riemer acquired the data, which K. Schneider, L. Michels, M. Kirschner, A. Burrer and S. Kaiser analyzed. K. Schneider, L. Michels, E. Seifritz and S. Kaiser wrote the article, which all authors reviewed and approved for publication.

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Table 1: Demographics, psychopathological and clinical characteristics of study participants

Characteristic	Group; mean ± SD*		Statistical	
	Schizophrenia,	Control,		
Age, years	27.7 ± 7.2	30.6 ± 6.6	t (47)= 1.45	0.15
Sex, female:male	7:22	6:14	$\chi^2(1)= .21$	0.65
Education, years	11.4 ± 2.8	14.2 ± 2.5	U= 101.5	≤ 0.001
Smoking, pack years	5.7 ± 13.7	2.4 ± 4.8	U= 239.5	.25
Duration of illness, years	7.2 ± 7.1	-	-	-
Age of onset, years	21.0 ± 4.8	-	-	-
Chlorpromazine equivalents, mg/d	497.7 ± 407.4	-	-	-
BNSS score				
Apathy (motivation and pleasure)	15.5 ± 6.9	-	-	-
Diminished expression	8.6 ± 7.0	-	-	-
SANS score§				
Apathy	11.9 ± 5.6	-	-	-
Diminished expression	10.4 ± 9.6	-	-	-
PANSS score¶				
Positive	6.4 ± 2.5	-	-	-
Negative	12.0 ± 5.2	-	-	-
Disorganized	4.7 ± 2.0	-	-	-
Excited	4.5 ± 0.7	-	-	-
Depressed	5.4 ± 2.4	-	-	-
Total	47.7 ± 10.2	-	-	-
CDSS total score	2.1 ± 2.5	-	-	-
GAF score	58.1 ± 9.6	-	-	-
PSP total score	58.2 ± 9.1	-	-	-
MWT IQ	24.52 ± 6.03	28.70 ± 2.79	t (47)= 2.89	0.006

BNSS= Brief Negative Symptom Scale; CDSS= Calgary Depression Scale for Schizophrenia; GAF= Global Assessment of Functioning; MWT IQ= Multiple Word Test Intelligence Quotient; PANSS= Positive and Negative Syndrome Scale; PSP= Personal and Social Performance Scale; SANS= Scale for the Assessment of Negative Symptoms; SD= Standard deviation.
*Unless otherwise indicated.
§Apathy includes avolition/apathy and anhedonia/asociality; diminished expression includes affective flattening or blunting and alogia.
¶Positive factor= P1, P3, P5, P9; negative factor= N1, N2, N3, N4, N6, G7; disorganized factor= P2, G5, N11; excited factor= P4, P7, G8, G14; depressed factor= G2, G3, G6.
**Cognition data have been *z*-transformed based on the data of the control group for each test separately. The composite cognitive ability score was computed as the mean of the *z*-transformed test scores at the participant level.

Table 2: Mean rCBF values per ROI and group in mL/100g/min

	Patients		Healthy Controls		Statistical test
	Mean	SD	Mean	SD	
VS	33.8	7.9	31.5	9.3	t (47)= -.91, p= .37
DS	28.4	9.1	26.1	7.8	t (47)= -.95, p= .35

rCBF= regional cerebral blood flow; ROI= region of interest; VS= ventral striatum; DS= dorsal striatum; SD= standard deviation.

Table 3: Spearman correlations between apathy and diminished expression with the left and right VS and DS

	Apathy		Diminished expression	
	r_s (df = 27)	p	r_s (df = 27)	p
mean rCBF VS left+right	.38	.04	.02	.91
mean rCBF DS left+right	.48	.008	.17	.39
mean rCBF left VS	.32	.09	.009	.96
mean rCBF right VS	.40	.03	.003	.99
mean rCBF left DS	.44	.02	.19	.32
mean rCBF right DS	.51	.005	.10	.61

rCBF= regional cerebral blood flow; VS= ventral striatum; DS= dorsal striatum; r_s= Spearman correlation coefficient; df= degree of freedom.

Table 4: Spearman correlations between striatal rCBF and confounding variables as well as PANSS negative factor scores in patients with schizophrenia

	mean rCBF ventral striatum		mean rCBF dorsal striatum	
	r_s (df= 27)	p	r_s (df= 27)	p
PANSS positive factor	-.15	.44	-.24	.21
PANSS negative factor	.17	.39	.30	.12
CDSS total score	.23	.24	.35	.06
Chlorpromazine equivalents	-.05	.80	-.17	.39
Composite cognitive ability score	.27	.17	.11	.58
Age	-.39	.04	-.50	.006

PANSS= Positive and Negative Syndrome Scale; CDSS= Calgary Depression Scale for Schizophrenia; rCBF= regional cerebral blood flow; r_s= Spearman correlation coefficient; df= degree of freedom.

Figure 1: Region of interest (ROI) of the ventral (A) and dorsal (B) striatum.

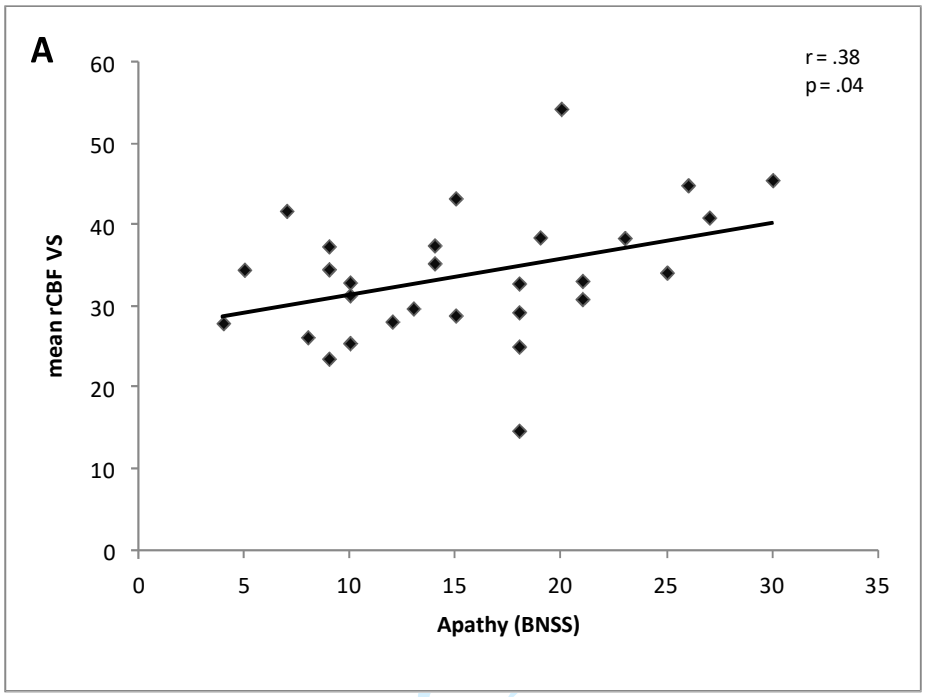

Figure 2A: Spearman correlation (including significance test) of mean regional cerebral blood flow (rCBF) of the left and right ventral striatum (VS) with apathy. BNSS = Brief Negative Symptom Scale.

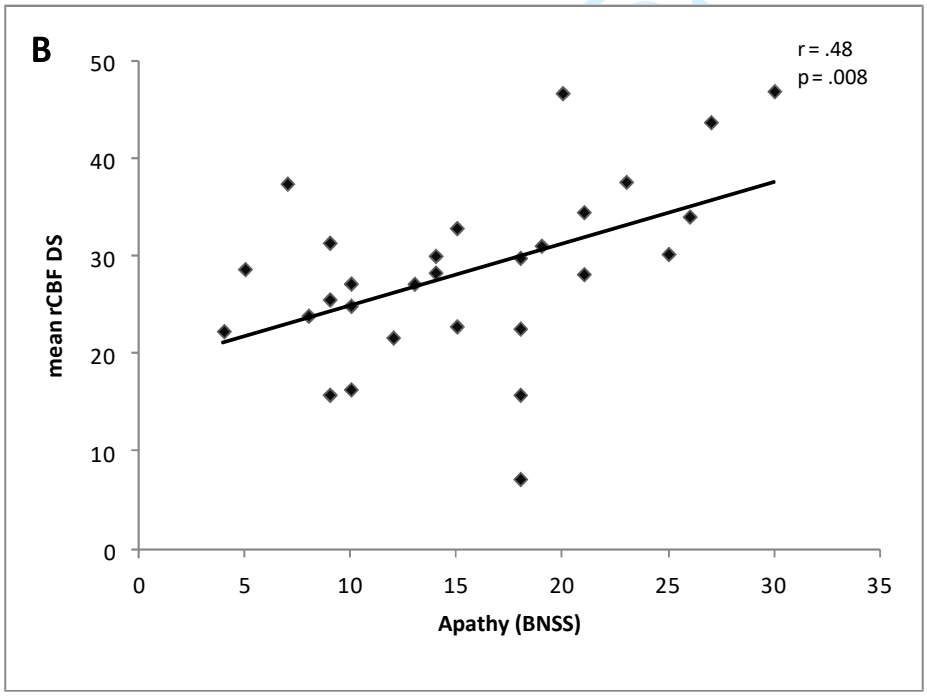

Figure 2B: Spearman correlation (including significance test) of mean regional cerebral blood flow (rCBF) of the left and right dorsal striatum (DS) with apathy. BNSS = Brief Negative Symptom Scale.

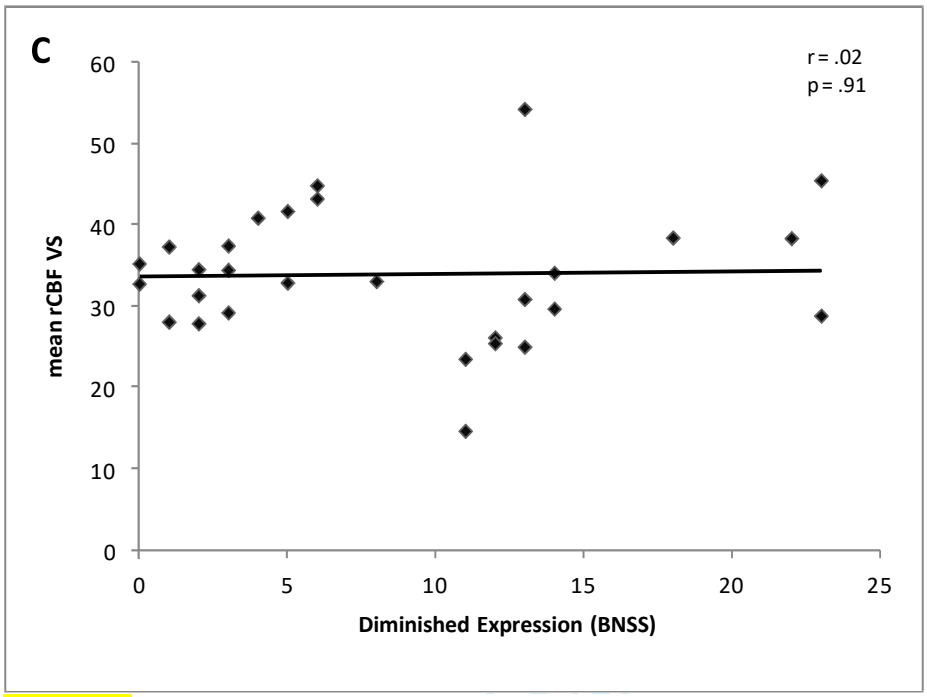

Figure 2C: Spearman correlation (including significance test) of mean regional cerebral blood flow (rCBF) of the left and right ventral striatum (VS) with diminished expression. BNSS = Brief Negative Symptom Scale.

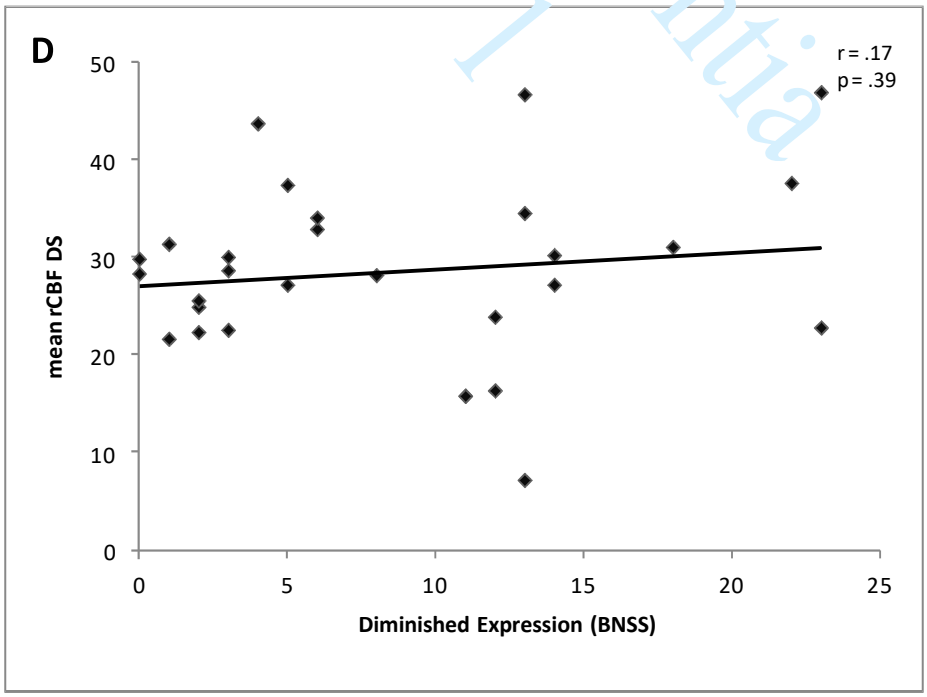

Figure 2D: Spearman correlation (including significance test) of mean regional cerebral blood flow (rCBF) of the left and right dorsal striatum (DS) with diminished expression. BNSS=Brief Negative Symptom

Scale.

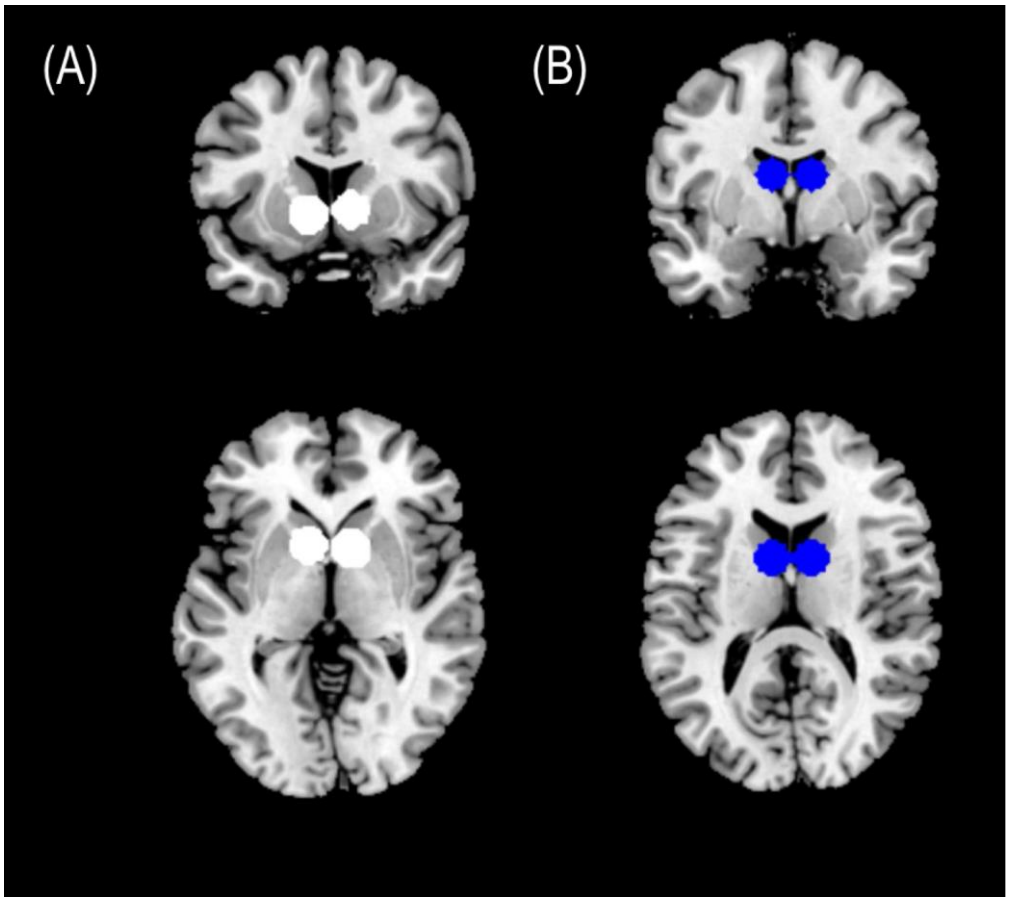

Figure 1: Region of interest (ROI) of the ventral (A) and dorsal (B) striatum.
322x287mm (300 x 300 DPI)